T7107

Exploring Dissolution, Supersaturation and Precipitation of Posaconazole in the Gastrointestinal Simulator (GIS) In Parallel With Visualization of Precipitated Drug by Microscopy Studies

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PURPOSE

- The aim of this study was **to evaluate the *in vivo* performance of four different oral formulations of posaconazole in the Gastrointestinal Simulator (GIS), a formulation predictive dissolution (fPD) apparatus. Coupled with *in vitro* dissolution testing, a computational model was applied to simulate plasma profiles**. In addition, **the morphology and the appearance of formed precipitate of posaconazole was evaluated by polarized optical microscopy (POM).**
- **Intraluminal and systemic concentrations of posaconazole for the different formulations** served as reference data to compare between *in vitro* and *in vivo* data (Hens et al. 2016 - DOI: https://doi.org/10.1002/jps.24690 and https://doi.org/10.1016/j.xphs.2016.03.027).

METHOD

- Four oral formulations **- one solution (20 mg of posaconazole dissolved in 240 mL of tap water, pH 1.6), two suspensions (40 mg of posaconazole dispersed in 240 mL of water; pH 1.6 and 7.1) and one solid dispersion of posaconazole (100 mg)** - were **evaluated in the GIS**, a three-compartmental *in vitro* dissolution device: **concentrations of posaconazole** (i.e. solution concentrations, total concentrations and thermodynamic solubility) were determined in **the gastric, duodenal and jejunal compartments (Figure 1)**. Gastric emptying followed a first order emptying rate with a gastric half-life of 13 min. Duodenal volume was kept constant during the entire experiment.

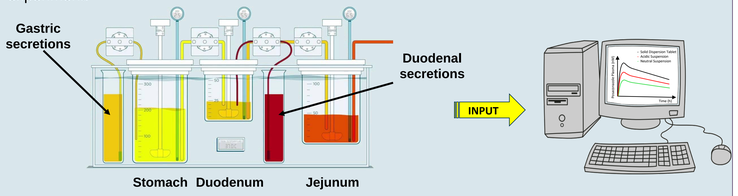


Figure 1: Setup and design of the GIS that was applied to test the different formulations of posaconazole in fasted state conditions coupled with a computational model to predict plasma profiles.

Fasted State Test Conditions	Stomach	Duodenum	Jejunum
Dissolution Media	Simulated Gastric Fluid (SGF), 0.01 M HCl (pH 2.0)	Phosphate buffer, pH 7.5 – 100 mM	/
Initial Volume	60 mL of SGF w/ 240 mL of liquid formulation or 240 mL of tap water in case of the tablet	50 mL	/
Secretions	1 mL/min of SGF	1 mL/min of Phosphate buffer, pH 7.5 – 200 mM	/

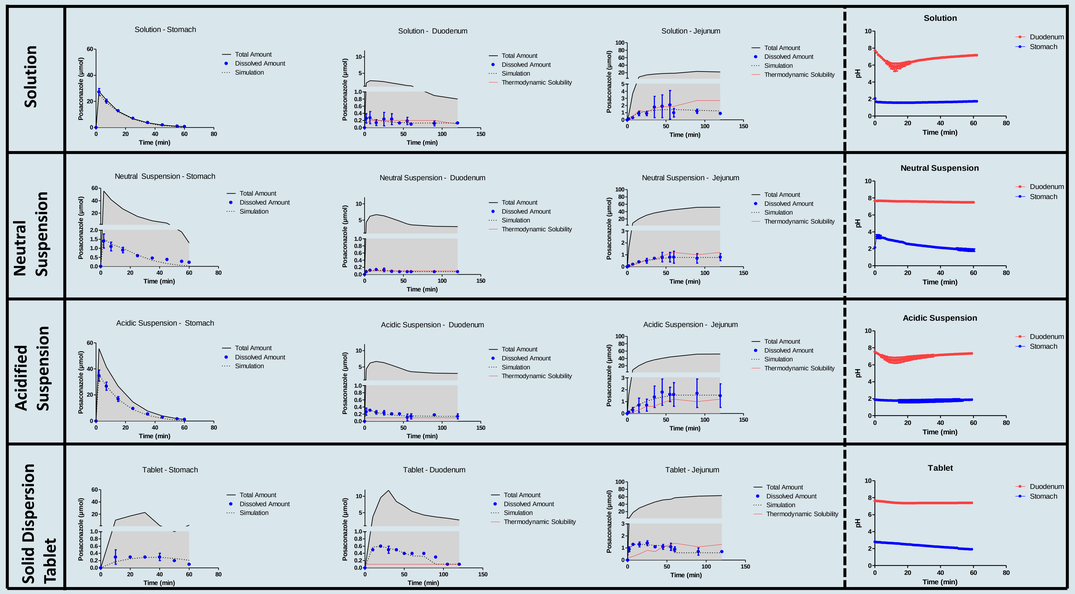
Table 1: Fasted state experimental conditions in each compartment for testing the different drug formulations of posaconazole in the GIS.

- **A computational approach (two compartmental model) has been applied to describe the *in vitro* dissolution and precipitation kinetics of posaconazole** for the different drug formulations in parallel with simulating the systemic profiles by implementing physicochemical, absorption and disposition properties related to posaconazole. The setup of the model is analogous to the model described by Matsui et al.[2] **Predicted plasma concentration profiles of posaconazole were compared with the observed human plasma profiles to evaluate the performance of the formulations *in vitro* and *in vivo*.**

- To visualize the appearance and morphology of the **precipitation behavior of posaconazole in different test conditions**, ***in situ* microscopy studies** were conducted to gain information about the appearance of the formed precipitate. Transfer experiments were performed in a **96-well plate** by adding 150 µL of liquid formulation (solution or suspension) directly into 150 µL of 200 mM phosphate buffer (pH 7.5), mimicking the GIS experimental conditions. Pictures were taken as a function of time to visualize precipitation up to 24 h. **Solid-state characteristics were evaluated by using polarized optical microscopy (POM)** (Leica, DMPL, Bannockburn, IL).

RESULTS

Figure 2: Solution concentrations (blue line with circles; ○), total concentrations (gray area) and thermodynamic solubility (red line) of posaconazole after exploring the solution (20 mg), neutral suspension (pH 7.1; 40 mg), acidified suspension (pH 1.6; 40 mg) and the solid dispersion tablet (100 mg) in the GIS. Fitted curves are given by the black dotted line. The extreme right curves show the pH profiles in the gastric and duodenal chamber of the GIS device. The simulated profiles served as input for the computational model to simulate plasma profiles. Solution concentrations and pH values are presented as mean ± S.D.



Pharmacokinetic (PK) Parameters	Value	References
V_c (L)	61.15	Derived from fitted data for 50 mg IV dosis (Kersemaekers et al. 2015)
k_a (h^{-1})	0.17	Derived from fitted data for 50 mg IV dosis (Kersemaekers et al. 2015)
k_{12} (h^{-1})	3.14	Derived from fitted data for 50 mg IV dosis (Kersemaekers et al. 2015)
k_{21} (h^{-1})	1.10	Derived from fitted data for 50 mg IV dosis (Kersemaekers et al. 2015)
Clearance (L/h)	10.5	Derived from fitted data for 50 mg IV dosis (Kersemaekers et al. 2015)
P_{eff} (cm/h)	2.31	Hens et al. 2017

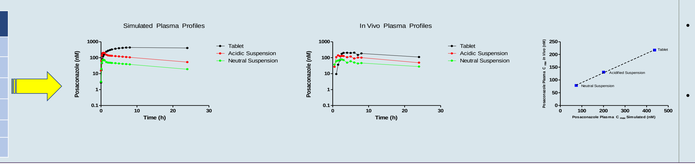
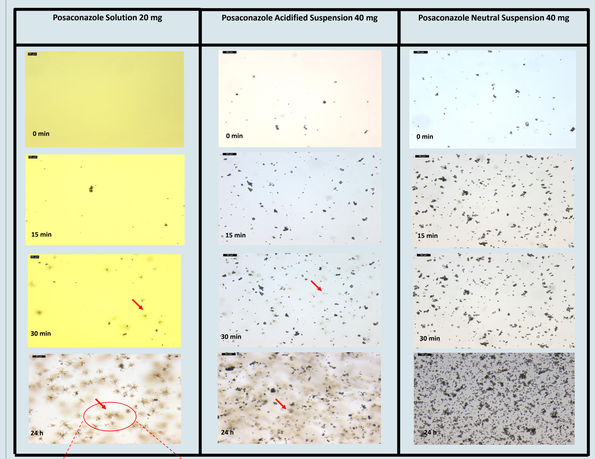
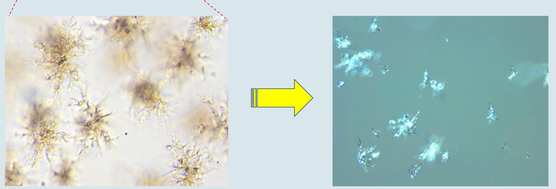


Figure 3: Morphology and appearance of posaconazole suspended particles and formed precipitate as a function of time, up to 24 h. Polarized optical microscopy (POM) demonstrated the crystalline appearance of the formed precipitate.





- To test the **precipitation-inhibiting effects of HPMC-AS** (which is the present polymer in the solid dispersion tablet), a comparison was made to look at the time of appearance of these crystal structures for a 10 mg solution of posaconazole (pH 1.6) that was transferred directly to 200 mM phosphate buffer (1:1 dilution) in presence (0.05%) and absence of HPMC-AS. **The appearance of the small crystals was delayed with 40 min in presence of the polymer, which demonstrates the precipitation-inhibiting effects of the polymer.**
- This **technique opens horizons for looking at the morphology and appearance of precipitation for poorly soluble BCS class 2b compounds in presence and absence of a precipitation-inhibitors.** This will give a **more rational approach to evaluate the precipitation properties of a compound** and, moreover, **which precipitation-inhibitor is the most favorable to delay precipitation.**

CONCLUSION & FUTURE DIRECTIONS

Testing different oral formulations of posaconazole in the GIS coupled with computational modeling **showed to be successful in order to discriminate between the performance of these formulations**, based on and compared with the *in vivo* data. The extensive presence of solid/precipitated amount of posaconazole was visualized by microscopy studies, **showing the formation of crystal structures.** This may explain why **no re-dissolution of the precipitate was observed in the GIS after an initial phase of supersaturated concentrations.** Therefore, **the microscopy application** is **an added value** in the field of supersaturation/precipitation **for looking to the morphology and appearance of precipitated drug. Also, the effects of precipitation-inhibitors (e.g. polymers, surfactants, cyclodextrins) can be screened.**

FUNDING & ACKNOWLEDGMENT

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